Institution: The University of Manchester

Unit of Assessment: 1

Title of case study:
Developing the evidence base for a changing cervical screening programme in England

1. Summary of the impact

The results of two major randomised trials and a cohort study based at the University of Manchester (UoM) have had a major impact on cervical screening in the UK and influenced thinking internationally. These trials evaluated two technologies which had the potential to improve cervical screening. As a result HPV primary screening has moved to a large national pilot study. HPV as a test of cure following treatment of cervical precancerous lesions has now been adopted as standard across the National Screening Programme. Automation assisted technology, which was shown to be inferior to manually read cytology, will not be adopted.

2. Underpinning research

See section 3 for references 1-6. UoM researchers are given in bold.

Key UoM researchers:

- **Henry Kitchener** (Professor of Gynaecological Oncology, 1996-date)
- **Graham Dunn** (Professor of Biostatistics,1996-date)
- **Chris Roberts** (Senior Research Fellow, 1997; Senior Lecturer, 1997-2004; Professor of Biostatistics, 2004-date)

Two trials led by **Kitchener**, together with **Dunn** and **Roberts**, formed the basis of this research. Both trials were funded by the NIHR Health Technology Assessment (HTA) Programme (2001-2009).

ARTISTIC: HPV Testing

The first was a primary cervical screening trial (ARTISTIC) involving 24,000 women, which compared cytology alone with cytology combined with HPV testing. HPV testing was performed on the cytology-only arm but the results were concealed and did not influence management. This study produced a large powerful dataset of cytology and HPV (including comprehensive genotyping) and histopathology outcomes, which informed not only a robust trial result, but also important data which allowed comparison of the performance of cytology and HPV testing over the six years of three screening rounds (2001-9).

The results of the trial (1) and an NIHR HTA Monograph (2) showed that combining HPV and liquid based cytology did not detect more high grade cervical intraepithelial neoplasia than liquid based cytology over two rounds but it did result in a reduction in high grade CIN in the second round. This trial is only one of the several major RCTs internationally which involved liquid-based cytology and is the only one to be extended to three rounds. Following completion of the third round, we showed very convincingly that HPV baseline screening is as protective over six years as cytology was over three years (3). ARTISTIC has now been included in a pooled analysis of four European trials which has shown a reduction in the incidence of cervical cancer following HPV screening (4).

MAVARIC: Automated Assisted Reading

The second study, also funded by the NIHR HTA programme, was a randomised trial led from Manchester, which compared conventionally read slides with automated assisted reading and involved 75,000 randomised samples from women in Greater Manchester undergoing primary cervical screening between 2006 and 2009. It was the most robustly designed study to date, using histopathology rather than cytology outcomes as the primary endpoint. It produced a clear cut result showing that automated reading was 8% less sensitive, relative to manual reading and was thus considered inferior. One of the two commercial systems has the ability to file around one quarter of slides as normal, requiring no human reading (5). This ‘No further review’ facility was

found to be very reliable and could be recommended for use in the NHS based on its ability to reduce staff time and costs.

In addition to ARTISTIC and MAVARIC, a prospective study on the use of HPV testing to determine cure after treatment for cervical pre-cancer led by **Kitchener**'s team has also had significant impact. The study, funded by the NHS Cervical Screening Programme between 2004 and 2007, showed that the cumulative incidence of failed treatment in women who were cytology-negative/HPV-positive 6 months after treatment was low, such that treated women could be returned to 3-year recall instead of annual cervical cytology for 10 years. This system was adopted by the National Cervical Screening Programme in September 2012 (6).

3. References to the research

1. **Kitchener HC**, Almonte M, Thomson C, Wheeler P, Sargent A, Stoykova B, Gilham C, Baysson H, **Roberts C**, Dowie R, Desai M, Mather J, Bailey A, Turner A, Moss S, Peto J. HPV testing in combination with liquid-based cytology in primary cervical screening (ARTISTIC): a randomised controlled trial. *Lancet Oncology*. 2009;10(7):672-82. DOI: 10.1016/S1470-2045(09)70156-1

2. HTA Monograph:
Kitchener HC, Almonte M, Gilham C, Dowie R, Stoykova B. ARTISTIC: a randomised trial of human papillomavirus (HPV) testing in primary cervical screening. *Health Technology Assessment*. 2009;13(51):150.
DOI: 10.3310/hta13510

3. **Kitchener HC**, Gilham C, Sargent A, Bailey A, Albrow R, **Roberts C**, Desai M, Mather J, Turner A, Moss S, Peto J. A comparison of HPV DNA testing and liquid based cytology over three rounds of primary cervical screening: Extended follow up in the ARTISTIC trial. *European Journal of Cancer*. 2011;47(6):864-71.
DOI: 10.1016/j.ejca.2011.01.008

4. Ronco G, Dillner J, Elfström KM, Tunesi S, Snijders PJ, Arbyn M, **Kitchener H,** Segnan N, Gilham C, Giorgi-Rossi P, Berkhof J, Peto J, Meijer CJ; the International HPV screening working group. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet. 2013 Nov 1. pii: S0140-6736(13)62218-7. doi: 10.1016/S0140-6736(13)62218-7. [Epub ahead of print]

5. MAVARIC:
Kitchener HC, Blanks R, **Dunn G**, Gunn L, Desai M, Albrow R, Mather J, Rana DN, Cubie H, Moore C, Legood R, Gray A, Moss S. Automation-assisted versus manual reading of cervical cytology (MAVARIC): a randomised controlled trial. *Lancet Oncology*. 2011;12(1):56-64.
DOI: 10.1016/S1470-2045(10)70264-3

6. **Kitchener HC**, Walker PG, Nelson L, Hadwin R, Patnick J, Anthony GB, Sargent A, Wood J, Moore C, Cruickshank ME. HPV testing as an adjunct to cytology in the follow up of women treated for cervical intraepithelial neoplasia. *BJOG*. 2008;115(8):1001-7.
DOI: 10.1111/j.1471-0528.2008.01748.x

4. Details of the impact

See section 5 for corroborating sources S1-S4.

Context

Cervical screening has been based on cytology ('cervical smear') for over 50 years. Its principal strength is its specificity in detecting precancerous cells, but its sensitivity is thought to be in the range of 50-80%. Testing for human papillomavirus, the cause of cervical cancer, is more sensitive

whether in population screening or testing for residual disease following treatment. The hypothesis behind these studies was that HPV negative women are at very low risk, whereas further investigation can be concentrated on HPV positive women who are at risk of developing cervical neoplasia.

Pathway to Impact

The robustness of the findings of these studies was critical to the decisions made by the Advisory Committee for Cervical Screening who make recommendations to Ministers on changes to the Cervical Screening Programme.

Reach and Significance of the Impact

The results of these studies have fed directly into NHS policy in the following ways:

1. The ARTISTIC Trial directly influenced the decision to establish a large HPV primary screening pilot study which began in the second quarter of 2013. The notes of the UK National Screening Committee (UK NSC) meeting held on 25 April 2012 demonstrate that ARTISTIC informed the Committee's decision-making: 'Members were asked about the cost-effectiveness of HPV TaPS [Testing as Primary Screening]. [Committee member] said the ARTISTIC trial had looked at both clinical and cost effectiveness but further modelling would be needed as part of the feasibility study. The UK NSC agreed that there is enough evidence to suggest that HPV TaPS would be cost and clinically effective. It was agreed that the UK NSC should consult on a recommendation to approve HPV as a primary screen for cervical cancer and that the feasibility study should explore implementation issues including length of time before a re-screen following a HPV negative result.' (S1, p. 7)
2. The MAVARIC Trial directly influenced the decision not to adopt automated reading of cervical cytology in England, because it was less sensitive than manual reading (S2). The 'No further review' facility of the BD Systems was shown to be reliable and its use endorsed by the Advisory Committee for Cervical Screening (S3). The international reach of this study is exemplified by the findings having been accepted by the Health Council of the Netherlands, who have rejected automated screening (S4).
3. The favourable results of the test of cure study (6) directly influenced the decision to initiate HPV test of cure as standard in the cervical screening programme in England.

Kitchener has contributed significantly to the Cervical Screening Programme in other ways. He chairs the Department of Health Advisory Committee for Cervical Screening, which advises Government on the direction of the Programme. He also chaired the Steering Group of the pilot studies of HPV triage and test of cure, both of which are being rolled out nationally in 2011/12. He now chairs the Steering Group for the HPV primary screening pilot studies, which have received National Screening Committee and Ministerial approval and commenced in the English Screening Programme in the second quarter of 2013.

5. Sources to corroborate the impact

S1. ARTISTIC:
UK National Screening Committee Minutes from 25 April 2012 meeting (items 4.15 and 4.16, p. 7). http://www.screening.nhs.uk/meetings

S2. MAVARIC:
Summary note of the meeting of the Advisory Committee on Cervical Screening, 22 June 2011 (Item 11.1). Available from:
http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_131296.pdf

S3.MAVARIC:

Summary note of the meeting of the Advisory Committee on Cervical Screening, 2 December 2010 (Item 6.1). Available from: http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_126029.pdf

S4. MAVARIC:
Health Council of the Netherlands, Population screening for cervical cancer http://www.gezondheidsraad.nl/en/publications/population-screening-cervical-cancer (p. 51)